

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

## Management of Hepatitis C Virus Infection in Liver Transplant Recipients



Satheesh P. Nair, MD  
Professor of Medicine  
Director of Transplant Hepatology  
Methodist University Hospital  
University of Tennessee Health Science Center  
Memphis, Tennessee

### **G&H** How common is hepatitis C virus infection in liver transplant recipients?

**SPN** If a patient has active hepatitis C virus (HCV) infection at the time of liver transplantation, the infection will recur in almost all patients. Given that HCV infection is the most common indication for liver transplantation, this scenario is quite common in clinical practice.

### **G&H** Is infection due to preexisting HCV infection in the host or HCV transmitted from the donor?

**SPN** Infection is always due to preexisting HCV in the host. However, HCV-positive allografts can be used for transplantation to an HCV-positive recipient. Patients typically consent to receive an HCV-positive allograft at the time of listing for transplantation. The donor liver is then biopsied prior to transplantation to check for fibrosis, and many transplant centers will use the organ as long as there is no fibrosis. There are several reports, mainly in abstracts, showing that using an HCV-positive graft is safe. Genotype 2 or 3 HCV-infected recipients are not listed to receive HCV-positive allografts.

### **G&H** What factors affect the likelihood of HCV infection recurring post-transplantation?

**SPN** All patients with an active HCV infection at the time of transplantation will develop an infection post-transplantation. Infection can also recur in patients who are

on antiviral treatment at the time of transplantation, even if their HCV RNA levels are undetectable. If a patient has achieved sustained virologic response (SVR) prior to transplantation, then the risk of HCV recurrence is very low.

When HCV infection recurs, several factors could cause the infection to progress faster, potentially leading to more severe disease. Database studies suggest that poor donor quality—increased donor age, fatty liver disease, extended cold ischemia time, or prolonged cholestasis post-transplantation—can be associated with faster progression of HCV infection. Use of extended-criteria donors in HCV-infected patients with lower Model for End-Stage Liver Disease (MELD) scores (<20 points) should be discouraged.

Another important factor to consider is that acute rejection can accelerate the progression of HCV infection. Although it makes sense to minimize immunosuppression in the setting of active viral infection, maintaining very low levels of immunosuppressive drugs in HCV-infected patients could be counterproductive if patients develop rejection. Case-control data from my institution show that black patients have a faster rate of progression. Finally, a steroid-free immunosuppression regimen might slow the progression of HCV infection, in addition to offering other benefits such as decreased risks of diabetes and osteoporosis.

### **G&H** What are the possible consequences of HCV infection in liver transplant recipients?

**SPN** Approximately 20–30% of HCV-infected patients develop cirrhosis within 5 years after transplantation. In

contrast, it takes at least 20 years for HCV infection to progress to cirrhosis in nontransplant patients. Many of the factors mentioned above may contribute to the accelerated progression observed in the post-transplantation setting. Moreover, transplant recipients who develop cirrhosis decompensate faster and have a higher 5-year mortality rate than HCV-infected cirrhotic patients who do not undergo transplantation.

Unfortunately, many transplant recipients who develop cirrhosis are not candidates for retransplantation, and outcomes in patients who do undergo retransplantation are usually not good. The transplant center where I practice typically does not offer the option of retransplantation if a patient develops cirrhosis within 5 years of transplantation. We only consider retransplantation if the patient has other correctable issues, such as biliary complications during the first transplantation, or if the patient has achieved SVR with treatment but liver disease has progressed due to other issues.

Rarely, liver transplant recipients develop a particularly aggressive form of recurrence called fibrosing cholestatic HCV infection, in which patients have high levels of HCV RNA, elevated bilirubin levels, and progressive fibrosis that leads to graft loss in 1–2 years. Pooled data show that interferon-based regimens are not very useful in this setting. However, direct-acting antiviral (DAA) agents may be able to slow progression of this condition, at least in the initial phase, as DAA agents can arrest HCV replication within 1–2 weeks.

### G&H How can clinicians prevent HCV infection associated with organ transplantation?

**SPN** The most reliable way to prevent post-transplantation HCV infection is to cure the infection before transplantation. However, this approach is not feasible in patients who present with decompensated cirrhosis, as use of interferon is contraindicated in these patients (MELD score >18 points). In addition, SVR rates are typically lower in cirrhotic patients, especially patients infected with genotype 1 HCV. However, shorter-duration therapies and interferon-free therapies could alter the treatment landscape in the near future, perhaps allowing a larger number of patients to achieve SVR before transplantation. As I mentioned previously, merely achieving undetectable levels of HCV RNA while on treatment may not be sufficient to prevent recurrence of HCV infection post-transplantation.

Another novel way to prevent the graft from becoming reinfected post-transplantation is to use monoclonal antibodies targeting the HCV proteins that help the virus gain entry into hepatocytes. A phase II study of these antibodies showed some promise, but an effective regimen will require a DAA drug in addition to the antibody.

### G&H Does use of antiviral therapy reduce the occurrence of HCV infection in transplant recipients? Which regimens are most effective in this setting?

**SPN** There is a lack of consensus as to when antiviral therapy should be initiated following transplantation. Interferon-based antiviral therapy is not tolerated in the immediate post-transplantation period and therefore is not recommended unless there is severe recurrence or fibrosing cholestatic HCV infection. Other patients are typically evaluated for antiviral therapy around 6 months post-transplantation if there are no contraindications. Treatment is definitely encouraged in patients with genotype 2 or 3 HCV infection and in patients who have a history of response to treatment prior to transplantation. Some transplant centers delay treatment until these patients develop stage 2 fibrosis, but data show that achieving SVR in the post-transplantation setting can reduce the likelihood of progression of fibrosis. Given that 30–40% of patients with genotype 1 HCV infection will respond to interferon, I see no reason why treatment should be delayed.

Lack of response to treatment prior to transplantation does not mean that patients will fail to respond post-transplantation. Interleukin (IL)-28B data in the post-transplantation setting are intriguing, with studies showing that receiving an allograft with a favorable *IL-28B* genotype (such as CC) increases response rates even if the recipient's *IL-28B* genotype is unfavorable (ie, TT). Antiviral treatment is not considered in patients who have a contraindication to interferon, patients with active post-transplantation complications, and patients with prior severe side effects to interferon.

Once we have more effective regimens, almost all HCV-infected liver transplant recipients are likely to be treated. We will also see more clinicians using protease inhibitors in the post-transplantation setting once we gain more experience in this population. One of the principal concerns with these drugs is their possible interaction with immunosuppressive drugs such as cyclosporine, tacrolimus, and sirolimus. Given that cyclosporine drug levels are increased only 4-fold when this drug is coadministered with telaprevir (Incivek, Vertex; compared to a 70-fold increase for tacrolimus), cyclosporine seems to be an attractive choice for HCV-infected transplant recipients who are planning to use a protease inhibitor.

Any changes to a patient's immunosuppression regimen should be made carefully to avoid rejection, especially in a patient who is on stable immunosuppression. My personal bias is to continue the current immunosuppression at a lower dose and follow the drug levels. Fortunately, we can monitor levels of these drugs and adjust the patient's

regimen as needed. We have a few patients at my institution, all with advanced fibrosis, who are on these agents, and we have been able to manage their immunosuppression well. The protocol at my institution is to stop tacrolimus on Day 1 of protease inhibitor therapy and measure tacrolimus levels 3 and 7 days later, and then adjust the dose of tacrolimus according to the level. At least in the small number of patients we have seen, a tacrolimus dose of 0.5 mg once per week is sufficient to maintain a drug level of 3–5 ng/mL. Prospective studies are being planned that should shed more light on the safety and efficacy of protease inhibitor–based antiviral therapy in transplant recipients. In my experience with the first generation of protease inhibitors, anemia seems to be the biggest challenge in this population—not the interaction between antiviral therapy and immunosuppressive drugs.

### **G&H** How can a transplant patient's immunosuppression regimen be adjusted to reduce the risk of HCV infection?

**SPN** Our transplant center has a large amount of experience with steroid-free immunosuppression regimens. Steroids are completely avoided in these patients by using a potent anti-T-lymphocyte agent at the time of transplantation. In our analysis, patients who do not receive steroids show a trend toward slower HCV progression. However, several confounding factors can modify HCV progression, so retrospective analyses have limitations. Unfortunately, even small prospective studies are not very feasible in this setting, given that donor quality and surgical complications cannot be controlled. While a larger prospective study could settle this issue, I doubt such a study will ever be undertaken.

In the long term, use of lower-dose immunosuppression could potentially reduce progression of HCV infection, with the caveat that there is the risk of precipitating rejection. Data show that high-dose steroids or T-cell–depleting therapies, when used to treat rejection, are associated with faster progression of HCV infection. However, these agents are used in the setting of acute rejection, and the main culprit in these cases may be the rejection itself. At my center, we typically aim for tacrolimus levels less than 5 ng/mL and monitor patients carefully for any early signs of rejection.

### **G&H** What other steps can clinicians take to manage HCV infection in post-transplant patients?

**SPN** First, clinicians should not use poor-quality grafts in HCV-infected patients with low MELD scores. Second, low-dose immunosuppression can be used,

but transplant centers should have a system in place to recognize rejection early and prevent full-blown rejection; clinicians need to be especially careful about rejection while immunosuppression is being lowered. Third, clinicians need to recognize severe recurrences early and offer treatment. Finally, every HCV-infected patient should be considered for treatment once they have recovered from transplantation and are on a stable immunosuppression regimen (usually about 6 months post-transplantation).

Another caveat is that clearance and effectiveness of tacrolimus are greatly influenced by liver function. For example, if a patient has a severe HCV recurrence and a high bilirubin level, the tacrolimus level will increase due to hepatic dysfunction, and often the dose of tacrolimus will be reduced. Once the HCV infection is treated and liver function improves, then tacrolimus levels can fall precipitously, which could trigger rejection if the tacrolimus dose is not re-increased. Also, based on the experience at my center and reported case series, the incidence of rejection seems to be slightly higher during interferon treatment, especially at the point when HCV RNA levels become undetectable. Patients may therefore require slightly higher doses of immunosuppression during this period.

### **G&H** What are the typical long-term outcomes when such cases are managed appropriately?

**SPN** In patients who achieve SVR in response to antiviral treatment, survival rates should be similar to those of transplant recipients who are not HCV-infected. As more clinicians become comfortable using DAA agents in the post-transplantation setting, we will likely be able to achieve this goal in many more patients. Also, clinicians should note that progression of fibrosis is occasionally observed even in patients who responded to treatment; in these cases, progression may be related to other factors, such as smoldering rejection, nonalcoholic steatohepatitis, other graft-related issues, or older donor or patient age.

### **G&H** What further research is needed to reduce the incidence of HCV infection in transplant recipients?

**SPN** We need to develop a protocol that allows new agents such as telaprevir and boceprevir (Victrelis, Merck) to be used effectively with interferon. With the rapid development of effective DAA agents, future interest and studies will focus on the timing and safety of these agents. In general, many of the factors related to immunosuppression and transplantation will likely

become less important if the vast majority of HCV-infected patients can be effectively treated. It will be interesting to see whether effective and safe therapies in the future can improve liver failure and avoid the need for transplantation altogether.

### Suggested Reading

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